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1 593 851

PATENT SPECIFICATION (11) 1 593 851

(21) Application No. 44649/76 (22) Filed 27 Oct. 1976
(61) Patent of addition to No. 1507462
(23) Complete Specification filed 6 Oct. 1977
(44) Complete Specification published 22 July 1981
(51) INT CL³ C07D 211/06 A61K 31/445
(52) Index at acceptance
C2C 1532 200 215 220 222 226 22Y 250 251 25Y 280 281 29X 29Y 30Y 311 313 314 31Y 321 322 323 32Y 332 338 342 34Y 364 36Y 57Y 603 620 624 62X 630 63X 660 662 694 697 699 802 80Y AA KH KZ

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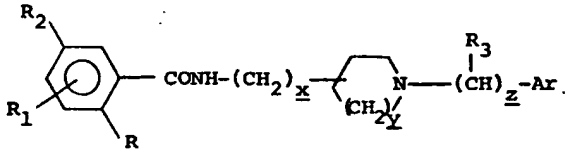
(54) N-(4-PIPERIDYL)-BENZAMIDES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(71) We, ANTONIO GALLARDO S.A., a Spanish Body Corporate of Cardoner 68—74, Barcelona 12, Spain, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described by which it is to be performed, to be particularly described in and by the following statement:—

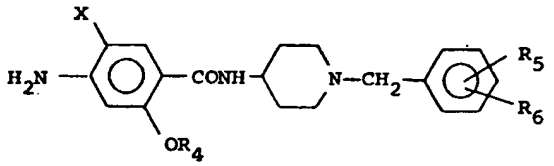
This invention relates to N-(4-piperidyl)-benzamides and to pharmaceutical compositions containing them. It is an improvement in or modification of the invention described and claimed in the Specification of our British Patent Applications Nos. 12572/74 and 35402/74 (granted as Patent No. 1,507,462).

In the Specification of British Patent No. 1,507,462 we have described and claimed compounds of the general formula:



I

(wherein R is a C_1—C_6 alkoxy or C_2—C_6 alkenoxy group; R_1 and R_2, which may be the same or different, are chosen from hydrogen (provided that R_1 and R_2 are not both hydrogen), halogen, sulphonamido, amino, (C_1—C_6)-alkyl- or di-(C_1—C_6)-alkyl-amino, alkylsulphonyl, mono- or di-alkyl-sulphonamido or acylamino groups, the radical R_1 being positioned at the 3 or 4-position of the aromatic ring; R_3 is hydrogen, a C_1—C_6 alkyl or optionally substituted aryl group, provided that, where z is greater than 1, R_3 is hydrogen or two groups R_3 on adjacent C-atoms form a bond between the said C-atoms with any remaining groups R_3 being hydrogen; Ar is an optionally substituted aryl, aroyl or single ring aromatic heterocyclic group, x is 0 or 1; y is 2 or 3; and z is an integer from 1 to 6, with the exclusion of those compounds of the general formula:—



II

wherein X is chlorine or bromine, R_4 is a straight- or branched-chain alkyl group containing up to six carbon atoms, R_5 and R_6 are hydrogen atoms, or one of those symbols is chlorine in the 3- or 4-position of a methyl or methoxy group in the 4-

position and the other symbol is a hydrogen atom, or R_2 and R_3 together represent a methylenedioxy group attached to the 3- and 4-positions) or a pharmaceutically acceptable salt or N-oxide derivative thereof. The compounds are stated to have useful pharmacological properties and, more particularly, the ability to antagonise the effects of dopamine or dopaminergic agents of endogenous or exogenous origin.

The compounds of general formula II are described and claimed in the Specification of our British Patent No. 1,507,463.

It has now been found that certain compounds falling within the scope of general formula I but which are not specifically disclosed in the specification of Applications Nos. 12572/74 and 35402/74 (Patent No. 1,507,462) possess the aforesaid pharmacological properties and also properties not hitherto disclosed in respect of compounds of general formula I.

The new compounds of the present invention are N - [1 - (*m* - trifluoromethylbenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - ethoxy - 4 - amino - 5 - chlorobenzamide, N - [1 - (2 - methoxy - 5 - chlorobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, N - [1 - (β - naphthylmethyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, N - [1 - (*p* - bromobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, N - [1 - (*p* - fluorobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, N - [1 - (*o* - methylbenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4,5 - diaminobenzamide, N - [1 - (*p* - nitrobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - bromobenzamide, N - [1 - (*m* - methylbenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, N - (1 - benzylpiperid - 4 - yl) - 2 - ethoxy - 4 - amino - 5 - chlorobenzamide, N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - methoxy - 4,5 - diaminobenzamide, N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - dimethylamino - 5 - chlorobenzamide, N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - methoxy - 4 - acetamido - 5 - aminobenzamide, N - (1 - benzylpiperid) - 2 - methoxy - 4 - methylamino - 5 - chlorobenzamide, N - (1 - benzylpiperid - 4 - yl) - 2 - allyloxy - 4 - amino - 5 - chlorobenzamide, N - (1 - *p* - methylbenzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - aminobenzamide, N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - aminobenzamide, N - [1 - (2 - methoxy - 5 - chlorobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - acetamido - 5 - aminobenzamide and N - (1 - benzylpiperid - 4 - yl) - 2 - ethoxy - 4 - methylamino - 5 - chlorobenzamide and pharmaceutically acceptable acid addition salts thereof. These compounds have been found to possess—in addition to the pharmacological properties mentioned in our earlier patent—new activities, the most interesting of which are anorexia (mouse spaghetti test) without amphetamine-like stimulation of the central nervous system, vasodilatation (mouse ear test) and inhibition of gastric acid secretion (pyloric ligature model of Shay) and ulcer formation (phenylbutazone or stress models) in the rat.

The new compounds may be prepared by application of the methods described in the specification of Applications Nos. 12572/74 and 35402/74 (Patent No. 1,507,462) for the preparation of compounds of general formula I. Their acid addition salts may be prepared by reacting the bases in a solvent such as methanol, ethanol, acetone or water, or a suitable mixture of such solvents, at a temperature between 10°C and the boiling point of the reaction mixture.

The present invention also includes within its scope pharmaceutical compositions comprising one or more of the afore-named compounds, or a pharmaceutically acceptable acid addition salt thereof, in association with a pharmaceutical carrier. The pharmaceutical carrier may be a solid, a liquid or a mixture of a solid and a liquid, and the compositions of this invention may be adapted for oral, rectal or parenteral use, the preferred method of administriation being *per os*. In this case, the compositions may take the form of tablets, capsules, lozenges, effervescent granules, syrups or suspensions. Such compositions may be made by methods well known in the art.

The following Example illustrates the preparation in detail of one of the compounds of the invention. Other compounds of the invention may be prepared in a similar manner.

EXAMPLE

N - [1 - (*m* - Trifluoromethylbenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide

To a suspension of 6.0 g of 2 - methoxy - 4 - amino - 5 - chlorobenzoic acid in 400 ml of anhydrous tetrahydrofuran, a solution of 4.2 ml of triethylamine in 28 ml of tetrahydrofuran was added. The resulting solution was cooled to −10°C and then a solution of 2.98 ml of ethyl chloroformate in 25 ml of tetrahydrofuran was slowly added. The mixture was stirred at the same temperature for half an hour and a solution of 8.58 g of 1 - (*m* - trifluoromethylbenzyl) - 4 - aminopiperidine in 25 ml of tetrahydrofuran was added. After stirring for 1 hour at −10° to −5°C, the temperature was allowed to rise to room temperature and the reaction mixture was left to stand overnight. The mixture was evaporated to dryness and the residue dissolved in a mixture of chloroform and water. The mixture was made strongly basic with sodium hydroxide solution, the chloroform phase was separated and washed with water, dried (sodium sulphate) and evaporated to dryness to yield 9.5 g of the title compound, m.p. 138—140°C (after crystallization from acetone/n-hexane). Its hydrochloride melted at 219—221°C.

By a similar procedure and using appropriate starting materials and appropriate quantities thereof, the following compounds were prepared:—

N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - ethoxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 282—284°C;

N - [1 - (2 - methoxy - 5 - chlorobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 200—203°C;

N - [1 - (β - naphthylmethyl)piperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 220—221°C;

N - [1 - (*p* - bromobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 242—243°C;

N - [1 - (*p* - fluorobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride monohydrate of which melts at 256—258°C (dec.);

N - [1 - (*o* - methylbenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide the hydrochloride of which melts at 186—188°C;

N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4,5 - diaminobenzamide, the hydrochloride monohydrate of which melts at 244—246°C;

N - [1 - (*p* - nitrobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 223—225°C;

N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - bromobenzamide, the hydrochloride of which melts at 239—241°C;

N - [1 - (*m* - methylbenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 217—219°C;

N - (1 - benzylpiperid - 4 - yl) - 2 - ethoxy - 4 - amino - 5 - chlorobenzamide, the hydrochoride of which melts at 271—273°C;

N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - methoxy - 4,5 - diaminobenzamide, the dihydrochloride monohydrate of which melts at 246—248°C;

N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - dimethylamino - 5 - chlorobenzamide, the fumarate of which melts at 185—187°C;

Bis[N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - methoxy - 4 - acetamido - 5 - aminobenzamide]fumarate, m.p. 165—166°C;

N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - methylamino - 5 - chlorobenzamide, the fumarate of which melts at 221—222°C (dec.);

N - (1 - benzylpiperid - 4 - yl) - 2 - allyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 223°—225°C;

N - (1 - *p* - methylbenzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - aminobenzamide, the fumarate of which melts at 172—174°C (dec.);

N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - aminobenzamide, the fumarate of which melts at 177—179°C;

N - [1 - (2 - methoxy - 5 - chlorobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - acetamido - 5 - aminobenzamide, the fumarate of which melts at 182—184°C (dec.); and

N - (1 - benzylpiperid - 4 - yl) - 2 - ethoxy - 4 - methylamino - 5 - chlorobenzamide, the fumarate of which melts at 229—231°C (dec.).

WHAT WE CLAIM IS:—

1. N - [1 - (*m*-Trifluoromethylbenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide and pharmaceutically acceptable acid addition salts thereof.

2. N - [1 - (1 - Phenylethyl)piperid - 4 - yl] - 2 - ethoxy - 4 - amino - 5 - chlorobenzamide and pharmaceutically acceptable acid addition salts thereof.

3. N - [1 - (2 - Methoxy - 5 - chlorobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide and pharmaceutically acceptable acid addition salts thereof.

4. N - [1 - (β - Naphthylmethyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide and pharmaceutically acceptable acid addition salts thereof.

5. N - [1 - (*p* - Bromobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide and pharmaceutically acceptable acid addition salts thereof.

6. N - [1 - (*p* - Fluorobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide and pharmaceuticlly acceptable acid addition salts thereof.

7. N - [1 - (*o* - Methylbenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide and pharmaceutically acceptable acid addition salts thereof.

8. N - (1 - Benzylpiperid - 4 - yl) - 2 - methoxy - 4,5 - diaminobenzamide and pharmaceutically acceptable acid addition salts thereof.

9. N - [1 - (*p* - Nitrobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide and pharmaceutically acceptable acid addition salts thereof.

10. N - [1 - (1 - Phenylethyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - bromobenzamide and pharmaceutically acceptable acid addition salts thereof.

11. N - [1 - (*m* - Methylbenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide and pharmaceutically acceptable acid addition salts thereof.

12. N - (1 - Benzylpiperid - 4 - yl) - 2 - ethoxy - 4 - amino - 5 - chlorobenzamide and pharmaceutically acceptable acid addition salts thereof.

13. N - [1 - (1 - Phenylethyl)piperid - 4 - yl] - 2 - methoxy - 4,5 - diaminobenzamide and pharmaceutically acceptable acid addition salts thereof.

14. N - (1 - Benzylpiperid - 4 - yl) - 2 - methoxy - 4 - dimethylamino - 5 - chlorobenzamide and pharmaceutically acceptable acid addition salts thereof.

15. N - [1 - (1 - Phenylethyl)piperid - 4 - yl] - 2 - methoxy - 4 - acetamido - 5 - aminobenzamide and pharmaceutically acceptable acid addition salts thereof.

16. M - (1 - Benzylpiperid - 4 - yl) - 2 - methoxy - 4 - methylamino - 5 - chlorobenzamide and pharmaceutically acceptable acid addition salts thereof.

17. N - (1 - Benzylpiperid - 4 - yl) - 2 - allyloxy - 4 - amino - 5 - chlorobenzamide and pharmaceutically acceptable acid addition salts thereof.

18. N - (1 - *p* - Methylbenzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - aminobenzamide and pharmaceutically acceptable acid addition salts thereof.

19. N - (1 - Benzylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - aminobenzamide and pharmaceutically acceptable acid addition salts thereof.

20. N - [1 - (2 - Methoxy - 5 - chlorobenzyl)piperid - 4 - yl] - 2 - methoxy - 4 - acetamido - 5 - aminobenzamide and pharmaceutically acceptable acid addition salts thereof.

21. N - (1 - Benzylpiperid - 4 - yl) - 2 - ethoxy - 4 - methylamino - 5 - chlorobenzamide and pharmaceutically acceptable acid addition salts thereof.

22. A pharmaceutical composition which comprises an N - (4 - piperidyl) - benzamide claimed in any one of claims 1 to 12, or a pharmaceutically acceptable acid addition salt thereof, in association with a pharmaceutically carrier.

23. A pharmaceutical composition which comprises an N - (4 - piperidyl) - benzamide claimed in any one of claims 13 to 21, or a pharmaceutically acceptable acid addition salt thereof, in association with a pharmaceutical carrier.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1981
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.